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REVIEW

Metabolism is regulated by protein acetylation

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Abstract **Lysine acetylation, first identified in histones, was initially thought to be a posttranslational modification occuring only in eukaryotic cells that controlled gene transcription either via remodeling chromatin or altering the transcriptional machinery. Recent studies, however, have shown that acetylation is a well-conserved metabolic regulatory mechanism that plays critical roles in regulating and coordinating cell metabolism. Acetylation regulates metabolism through controlling gene transcription, altering the metabolic enzymes activity and possibly other functional aspects, of metabolic enzymes. In this review, we provide an overview of the roles and significance of acetylation in metabolic regulation.**

Keywords acetylation, metabolism, regulation

Linking acetylation to metabolism control

Histones are a family of proteins that exists only in eukaryotes and have major roles in maintaining chromosome integrity and in controlling gene expression. Lysine acetylation was first identified in histones about 50 years ago (Phillips, 1963; Allfrey et al., 1964) and its roles in transcriptional regulation, mainly through chromatin remodeling and modification of transcription factors, has been intensively explored (Grunstein, 1997; Zhao et al., 2005). Lysine acetylation's role in chromatin remodeling is well known, and the two classes of enzymes responsible for reversible acetylating and deacetylating proteins have been named as histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively, reflecting the fact that acetylation has been primarily described in histones. With more and more non-histone acetylation substrates identified nowadays, the nomenclature of lysine acetylases and deacetylases has evolved in a way that reflects the prevailing effect of acetylation in wider cellular functions (Tables 1, 2).

Sir2 (silent information regulator 2), a member of a protein complex that is responsible for gene silencing in *S.cerevisiae*, was the first non-nuclear deacetylase identified (Rine and Herskowitz,1987; Frye, 2000). Sir2 was later found to have NAD$^+$ dependent deacetylase activity (Chang and Min, 2002). Interestingly, overexpression of Sir2 results in a life span extension, not its novel deacetylase activity, caught the attention of researchers. Sir2 have been identified in different species and in mammals, there are 7 Sir2 homologs identified, named SIRT1-7, respectively (Dryden et al., 2003).

Table 1 Known lysine deacetylases (KDAC)

	Lysine deacetylases
Class I	HDAC1, HDAC2, HDAC3, HDAC8
Class II	HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, HDAC10
Class II	SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, SIRT7
Class IV	HDAC11

Table 2 Known lysine acetylases (KAT)

	Lysine acetylases
GNAT family	GCN5, PCAF
p300/CBP family	CBP, p300
MYST family	KAT5, MYST3, MYST4, MYST2, MYST1
Transcription factor related	KAT12, KAT4, ATF2
Nuclear receptor associated	KAT13A, KAT13B
others	KAT1, KAT9, KAT14, CDY1, CDY2A

The involvement in deacetylase activity of NAD$^+$, a molecule universally in energy metabolism in all life forms, inspired scientists to consider whether lysine acetylation could also exist in prokaryotes, the ancient and more primitive forms of life. The first example of lysine acetylation in metabolism control in prokaryotes was identified in

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Salmonella enterica. Acetyl-CoA synthetase (ACS) activity in this organism was found to be negatively regulated by reversible lysine acetylation (Wang et al., 2010). The acetylation of ACS is controlled by an acetyltransferase, Pat, and a NAD^{+} dependent deacetylase, CobB (Starai et al., 2002). This breakthrough, however, overshadowed by histone acetylation studies, was considered as an isolated case in prokaryotes and caught little attention. At the time few scientists agreed that lysine acetylation originated in prokaryotes, and even fewer thought that lysine acetylation would play a role in regulating metabolism.

Recent progress in proteomics methodology has give scientists the ability to profile acetylated proteins in both prokaryotes and eukaryotes on a cellular proteome-wide basis. Ground breaking work in profiling acetylated proteins has been carried out by Kim et al. in Yingming Zhao's group, now at University of Chicago, then at South-western Medical Center, USA. By employing affinity purification/enrichment of acetylated peptides from *M. musculus* liver cells and cultured H293T cells, followed by tandem LC separation and MS analysis, they identified over 300 acetylated peptides, corresponding to about 200 acetylated proteins (Kim et al., 2006). Although it was later proven that this pioneer study suffered from less than perfect techniques and was not even close to a complete identification of all acetylated proteins in mouse and human cells, their results for the first time, showed that acetylated proteins are involved in all aspects of cellular function, with histones and transcription factors accounting for only a small portion of acetylated proteins in cells. Obviously, the importance of acetylation in cellular function other than transcriptional control was largely overlooked, a notion was soon confirmed by the work carried out at the Max-Planck Institutes. Choudhary et al. (2009) in Matias Mann's group combined optimized affinity purification approaches developed by Kim et al. with MS technologies to identify more than 1700 acetylated proteins cell wide. They enriched acetylated peptides from trypsinized leukemia cell lysates using an anti-acetyllysine antibody, then separated peptides into fractions by isoelectric focusing to avoid interference frim high abundance acetylated peptides before the fractions were analyzed by tandem MS (Zhao et al., 2005).

Surprisingly, despite the fact that Choudhary et al. (2009) carried out detailed bioinfomatics analysis and successfully predicted that acetylation was involved in almost all aspects of cellular function, and the fact they showed that 43 of 50 major metabolic enzymes involved in energy metabolism are acetylated, they failed to point out that acetylation is a universal regulatory mechanism in metabolism. Fortunately, this concept was soon confirmed by two other studies. Zhang et al. in Yingming Zhao's group first realized that metabolic enzymes in central metabolic pathways of *E. coli* are heavily acetylated (Zhang et al., 2009). Almost simultaneously, a research group led by Dr. Shimin Zhao, Guoping Zhao, Kunliang Guan and Yue Xiong at Fudan University, China, discovered that acetylation is not only a conserved mechanism for metabolism regulation but also exerts its regulatory functions via distinct mechanisms (Zhao et al., 2005; Wang et al., 2010).

With the overall picture of functions of acetylation uncovered, we can now hypothesize that lysine acetylation first emerged from ancient prokaryotes mainly as a mechanism to regulate metabolism, and that acetylation of nuclear proteins and other proteins evolved later to meet other physiological needs of advanced living organisms (Fig. 1). This hypothesis, although supported by the fact that bacterial deacetylase CobB can deacetylate human acetylated proteins, requries additional experimental evidence to validate. Without doubt however, the importance of acetylation's roles in metabolic regulation should be investigated.

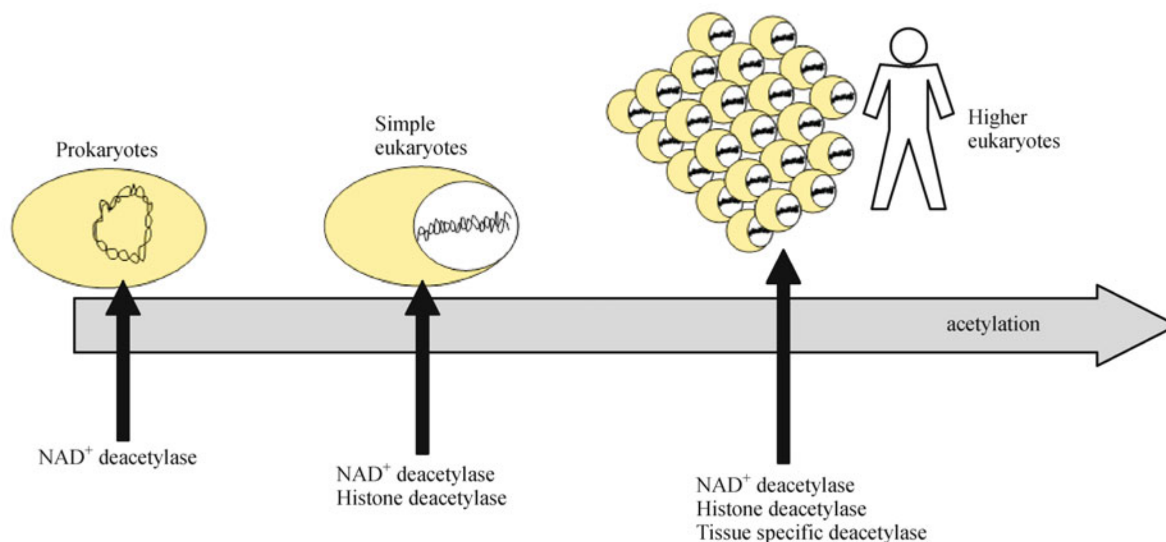

Figure 1 Evolvement of acetylation.

Acetylation regulates metabolism through gene transcription

Influenced by years of transcription regulation studies, acetylation's role in metabolism regulation was heavily studied at gene regulation level. Sirtuin 1 (SIRT1), the most heavily studied deacetylase in the Sirtuin family, exemplified how acetylation is involved in cholesterol synthesis, fatty acids metabolism, gluconeogenesis and insulin secretion.

SIRT1 has been found to control metabolism through multiple transcriptional mechanisms. SIRT1 deacetylation of the peroxisome proliferative activated receptor gamma coactivator 1 (PGC-1) is required for activation of mitochondrial fatty acid oxidation genes (Gerhart-Hines et al., 2007). Hepatic SIRT1 regulates lipid homeostasis by positively regulating peroxisome proliferator-activated receptor α (PPARα), a nuclear receptor that mediates the adaptive response to fasting and starvation. Hepatocyte-specific deletion of SIRT1 impairs PPARα signaling and decreases fatty acid β-oxidation, whereas overexpression of SIRT1 induces the expression of PPARα targets (Purushotham et al., 2009). SIRT1 also activates fat mobilization in white adipocytes in mammals. Mobilization of fatty acids from white adipocytes upon fasting is compromised in *sirt1*$^{+/-}$ mice (Picard et al., 2004). SIRT1 deacetylase activity and AMPK activity, which in turn reduce lipid accumulation in HepG2 hepatocytes exposed to elevated glucose, are activated by small molecule polyphenols (Feige et al., 2008). SIRT1 also suppresses expression of FAS (fatty acid synthase) and lipid accumulation through activating AMPK (Hou et al., 2008).

Other SIRT1 activators enhance endurance running performance and strongly protect from diet-induced obesity and insulin resistance by enhancing oxidative metabolism in skeletal muscle, liver, and brown adipose tissue (Feige et al., 2008). SIRT1 induces hepatic gluconeogenesis during fasting through the induction of genes encoding phosphoenolpyruvate carboxylase kinase (PEPCK), fructose-1,6-bisphosphatase (FBPase), and glucose-6-phosphatase (G6Pase) (Erion et al., 2009). In addition, SIRT1 controls gluconeogenic/glycolytic pathways in the liver in response to fasting signals through the transcriptional coactivator PGC-1 (Rodgers et al., 2005). Phosphorylation and function of another transcription factor, signal transducer and activator of transcription 3 (STAT3), are also tightly regulated in the liver through SIRT1-mediated deacetylation (Nie et al., 2009). A fasting-inducible switch, consisting of the histone acetyltransferase p300 and the nutrient-sensing deacetylase SIRT1, maintains energy balance in mice through the sequential induction of CREB regulated transcription coactivator 2 (CRTC2) and forkhead box O1 (FOXO1) (Liu et al., 2008). Lastly, SIRT1 transgenic mice display improved glucose tolerance due to decreased hepatic glucose production and increased adiponectin levels (Banks et al., 2008). Hepatic SIRT1 has also been shown to be a factor in systemic and hepatic glucose, lipid, and cholesterol homeostasis. Knockdown of SIRT1 in liver causes mild hypoglycemia, increased systemic glucose and insulin sensitivity, and decreased glucose production, adding to an already existing wealthy of data showing that SIRT1-mediated acetylation regulates metabolism-related transcription (Rodgers and Puigserver, 2007).

SIRT1 has also been found to be involved in the regulation of functions that are indirectly linked to metabolism. It was found as a positive regulator of liver X receptor (LXR) proteins, nuclear receptors that function as cholesterol sensors and regulate whole-body cholesterol and lipid homeostasis. Loss of SIRT1 *in vivo* reduces expression of a variety of LXR targets involved in lipid metabolism, including ABCA1, an ATP binding cassette (ABC) transporter that mediates an early step of HDL biogenesis (Li et al., 2007). SIRT1 knockdown also decreased serum cholesterol and increased hepatic free fatty acid and cholesterol content (Rodgers and Puigserver, 2007).

Acetylation regulates metabolic enzymes activities

After ACS activity of *Salmonella* was found to be negatively regulated by acetylation, the ACS activities of mammals and human were also found to be negatively regulated by acetylation (Hallows et al., 2006; Schwer et al., 2006). The fact that ACS of all species are universaly acetylated on active site lysine residues represents the first known example that a metabolic enzyme is regulated in the same way by acetylation in different species. Reports on the role of acetylation in the cytosolic gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK1) from different species, however, were different. In yeast, PEPCK1 catalytic activity was found to be negatively regulated by acetylation through lysine 514 acetylation. Acetylation of lysine 514 was shown to be crucial both for enzyme activity and for the ability of yeast to grow in non-fermentable carbon sources (Lin et al., 2009). On the other hand, we found that human PEPCK1, which shares limited amino acid sequence homology with yeast PEPCK1, is acetylated but that acetylation does not alter its specific activity. Instead, there was evidence that the protein stability of human PEPCK1 was affected (Zhao et al., 2010). That acetylation does not appear to be a conserved regulatory mechanism for PEPCK1 may be due to the fact that the two proteins studied so far are from very different origins. Among other enzymes whose activities are negatively regulated by acetylation are carbamoylphosphate synthetase 1 (CPS1), ornithine transcarbamoylase (OTC), long-chain acyl-coenzyme A dehydrogenase (LCAD) and isocitrate dehydrogenase 2 (IDH2) (Nakagawa et al., 2009; Yu et al., 2009; Hirschey et al., 2010). The common feature of these four enzymes is that they all located in mitochondria and thus the deacetylation processes are all mediated by a mitochondrial

deacetylase. CPS1 and OTC are urea cycle enzymes that involved in amino acids metabolism. Acetylation on CPS1 and lysine 88 of OTC results in reduced catalytic activity of these two enzymes. However, after deacetylation by SIRT3, a process controlled by amino acid availability in cells, the catalytic activities of both enzymes are restored (Yu et al., 2009; Nakagawa et al., 2009; Hirschey et al., 2010).

LCAD is hyperacetylated at lysine 42 in the absence of SIRT3. In the SIRT3 wild type mouse, LCAD is deacetylated under fasting conditions, which promote the utilization of fatty acids as energy source. However, mice lacking SIRT3 exhibit hallmarks of fatty-acid oxidation disorders during fasting, indicating that acetylation has a role in fatty acid metabolism (Hirschey et al., 2010). SIRT3 directly deacetylates and activates mitochondrial IDH2, leading to increased NADPH levels and an increased ratio of reduced-to-oxidized glutathione in mitochondria. Significantly, maintaining IDH2 activity is associated with age related hearing loss (Someya et al., 2010).

Notably, acetylation of metabolic enzymes does not always lead to reduced catalytic activity. Inhibition of deacetylase activity by TSA and NAM increases the activities of malate dehydrogenase (MDH) and the fatty acid metabolic enzyme enoyl CoA hydrotase/3-hydroxylacyl CoA dehydrogenase (EHHADH). This increase is not observed after the putative acetylated lysine residues are replaced by arginine. Both the acetylation level and enzymatic activity of MDH are stimulated by increasing glucose concentration in the culture medium. The same stimulation of acetylation level and enzymatic activity were also found in EHHADH after addition of fatty acids to the culture (Zhao et al., 2010). This evidence indicates that acetylation activates MDH and EHHADH.

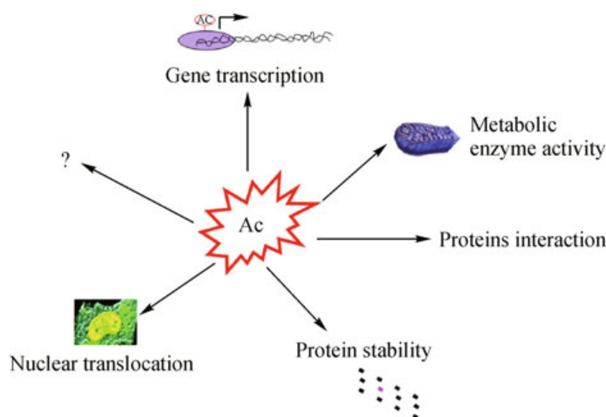

Figure 2 Acetylation involves in multiple cellular functions.

Table 3 Known metabolic genes that regulated by acetylation

Category	Genes
Transcription factors	*PGC-1*, *PPARα*, *STAT3*, *CRTC2*, *FOXO1*, *FXR*, *LXR*
Metabolic enzymes	*ACS*, *PEPCK1*, *GDH*, *IDH2*, *SOD*, *PEPCK*, *GAPDH*, *SDHA*, *ATP5B*, *CPS*, *OTC*, *LCAD*, *MDH*, *EHHADH*

Future directions of research into acetylation of metabolic enzymes

Although we now know that acetylation is involved in all aspects of metabolic regulation (Fig. 2; Table 3), research on acetylation's roles in regulation of metabolic enzymes remains in its infancy. However, many potentially interesting directions exist for further study. Principal among these is that, given that acetylation is well-characterized for metabolic enzymes, does it coordinate the activities of enzymes in metabolic networks? A coordinating role of acetylation in metabolism would certainly place the significance of acetylation on a higher level, given that complex diseases such as cancer and diabetes are all now known to be complex metabolic disorders. Another question is whether acetylation is connected to human disease? One of the exciting aspects of metabolic enzymes is that some, such as glyceraldehyde 3-phosphate dehydrogenase (GAPDH), can function as transcription factors. GAPDH was identified a transcription factor involved in S phase activation of the histone H2B OCA-S activation complex (Zheng et al., 2003). Notably, the acetyltransferase P300/CBP-associated factor (PCAF) acetylates GAPDH and induces its nuclear translocation. Nuclear translocation of GAPDH is mediated by acetylation of lysine residues 117, 227 and 251 lysine in humans (Ventura et al., 2010), providing a unique example of how acetylation regulates transcription directly via a metabolic enzyme. Another interesting aspect of acetylation is its action on TCA cycle enzymes such as isocitrate dehydrogenase 1 (IDH1), succinate dehydrogenase (SDH) and fumarate hydratase (FH). These are a group of metabolic enzymes that, once mutated, directly cause cancers (Briere et al., 2005; Ratcliffe, 2007). How these enzymes are regulated by acetylation, and whether dysregulation of these enzymes is involved in tumorigenesis, is of great interest.

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